International Journal of Health Sciences and Research
[Indexed, Peer-Reviewed Journal]
Volume 16; Issue: 2; February 2026
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

Stress Biomarkers in Acute Stroke: Cortisol as a Prognostic Indicator

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DOI: https://doi.org/10.52403/ijhsr.20260238

ABSTRACT

Acute ischemic stroke (AIS) provokes a significant systemic stress response marked by activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, resulting in elevated cortisol levels. Cortisol, the primary glucocorticoid hormone, regulates metabolic, immune, vascular, and neuronal functions during stress. While initially adaptive, excessive or sustained hypercortisolemia in AIS may contribute to secondary brain injury and unfavorable clinical outcomes.

Elevated cortisol promotes gluconeogenesis and insulin resistance, leading to stress hyperglycemia, which is associated with larger infarct size, blood–brain barrier disruption, and poorer neurological recovery. Cortisol also exerts immunosuppressive effects, reducing lymphocyte activity and altering cytokine balance, thereby increasing susceptibility to post-stroke infections such as pneumonia. Additionally, cortisol may impair endothelial function, increase oxidative stress, and disrupt cerebral autoregulation, further aggravating ischemic damage. At the neuronal level, excessive glucocorticoid exposure has been linked to excitotoxicity, mitochondrial dysfunction, and apoptosis.

Clinical studies consistently demonstrate that higher cortisol levels during the acute phase correlate with greater stroke severity, larger infarct volumes, increased complications, and poorer functional outcomes, including higher short-term mortality. Both serum and salivary cortisol have been explored as prognostic biomarkers; however, variability in sampling timing, circadian influences, and assay methods limits standardization.

Cortisol likely serves both as a marker of stroke severity and a mediator of secondary injury. Although promising as a prognostic indicator, further research is needed to clarify its causal role and therapeutic implications in AIS management.

Keywords: Acute ischemic stroke, cortisol, HPA axis, stress biomarkers, prognosis, neuroendocrine response

INTRODUCTION

Stroke remains one of the foremost causes of mortality and long-term disability worldwide, posing a substantial public health challenge. It is consistently ranked among the leading causes of death and contributes significantly to both years of life lost and years lived with disability. Although advancements in acute interventions, including thrombolysis and mechanical thrombectomy, have enhanced survival rates, the global burden of stroke continues to be considerable, particularly in low- and middle-income countries.

In addition to its impact on survival, stroke commonly leads to lasting neurological impairments such as motor deficits, speech and language difficulties, cognitive decline, and emotional disturbances. Many survivors face diminished functional independence and require prolonged rehabilitation and ongoing caregiver assistance. The financial consequences are also significant, encompassing high healthcare expenditures and reduced productivity.

Given that several major risk factors—including hypertension, diabetes, smoking, and obesity—are modifiable, effective prevention strategies and timely management are essential to lessen the worldwide burden of stroke [1].

Traditionally considered a focal cerebrovascular disorder limited to the brain, stroke is now increasingly recognized as a condition that provokes a broad systemic response beyond the ischemic region. Acute cerebral injury promptly engages central stress pathways, notably the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. Ischemic insult stimulates the hypothalamus to secrete corticotropin-releasing hormone (CRH), which triggers adrenocorticotropic hormone (ACTH) release from the pituitary gland, ultimately leading to cortisol secretion from the adrenal cortex. At the same time, sympathetic activation elevates circulating catecholamines, including adrenaline and noradrenaline.

This integrated neuroendocrine reaction is initially protective, helping to preserve cerebral perfusion, maintain hemodynamic stability, and mobilize metabolic substrates during acute stress. However, if excessive or sustained, such activation may result in metabolic imbalance, immune suppression, and progression of secondary brain injury. Therefore, stroke should be viewed not merely as a localized vascular event but also as a disorder characterized by significant systemic neuroendocrine stress activation [2,3].

Among biomarkers associated with the stress response, cortisol has gained particular interest due to its pivotal role in orchestrating physiological adaptations to stress and its consistent relationship with stroke severity and clinical outcomes. As the primary glucocorticoid hormone, cortisol modulates glucose metabolism, immune responses, vascular reactivity, and inflammatory signaling mechanisms that are profoundly disturbed in acute ischemic stroke (AIS). Its quantifiable rise during the acute phase and its association with established clinical indicators highlight its potential utility in prognostic evaluation and risk stratification.

Acute cerebral ischemia promptly stimulates hypothalamic stress pathways. Ischemic insult and altered intracranial signaling provoke the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which subsequently induces adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary gland. ACTH then acts on the adrenal cortex to promote cortisol release into the bloodstream. This activation of the hypothalamic–pituitary–adrenal (HPA) axis occurs in parallel with sympathetic nervous system stimulation, together constituting a coordinated neuroendocrine stress response. Although initially protective—supporting hemodynamic stability and metabolic demands—persistent elevation of cortisol may contribute to metabolic disturbances, immune dysfunction, and exacerbation of secondary neuronal damage in AIS [4].

Moreover, increased early cortisol has been associated with larger infarct sizes, a higher incidence of medical complications, and greater short-term mortality. Patients who exhibit persistently elevated cortisol levels tend to experience poorer functional recovery, diminished chances of regaining independence, and less favorable outcomes on follow-up scales such as the modified Rankin Scale.

Collectively, these observations suggest that early hypercortisolemia may function both as an indicator of stroke severity and as a potential contributor to secondary injury processes, thereby influencing overall recovery and survival [5–7]. Recognizing

cortisol as both a mediator and a marker of the stress response may improve prognostic evaluation in acute stroke management.

MATERIALS & METHODS

This review was conducted through a structured literature search to identify studies examining cortisol and its role in acute ischemic stroke (AIS). Databases including PubMed, Scopus, Web of Science, and Google Scholar were searched for relevant articles published in English up to 2025. Keywords and Medical Subject Headings (MeSH) used included "cortisol," "acute ischemic stroke," "hypothalamic–pituitary–adrenal axis," "stress response," "catecholamines," "inflammation," and "neuroendocrine."

Original research articles, clinical studies, observational studies, systematic reviews, and meta-analyses were included, while case reports, editorials, and studies unrelated to AIS or cortisol were excluded. The search strategy prioritized human studies but also included relevant experimental studies to provide mechanistic insights.

Data extraction focused on study design, sample size, timing and method of cortisol measurement, associations with stroke severity and outcomes, interaction with other biomarkers (e.g., catecholamines, IL-6, CRP), and potential clinical implications. Articles were critically appraised for methodological quality, relevance, and consistency of findings.

This narrative review synthesizes evidence regarding the pathophysiological role of cortisol in AIS, its prognostic significance, interactions with systemic inflammatory and autonomic markers, and potential implications for patient management and future research directions.

DISCUSSION

Physiology of the HPA Axis

The hypothalamic–pituitary–adrenal (HPA) axis is composed of three primary components: the hypothalamus, the anterior pituitary gland, and the adrenal cortex. Activation of this axis during stress begins with the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH acts on the anterior pituitary to stimulate the secretion of adrenocorticotropic hormone (ACTH). ACTH subsequently travels through the systemic circulation to the adrenal cortex, where it stimulates cortisol production in the zona fasciculata [8].

Cortisol secretion exhibits a distinct circadian rhythm governed by the suprachiasmatic nucleus (SCN) of the hypothalamus, the body's primary biological clock. In normal physiological states, cortisol levels start to increase in the early morning, peak shortly after awakening—referred to as the cortisol awakening response—and then progressively decline throughout the day, reaching their lowest levels around midnight. This diurnal variation plays a crucial role in maintaining metabolic balance, modulating immune function, regulating blood pressure, and synchronizing sleep–wake cycles.

In acute illnesses such as stroke, this circadian rhythm is frequently disrupted, reflecting dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and potentially influencing disease severity and recovery [9]. During acute stress, circadian regulation may be overridden, leading to transient hypercortisolemia. Cortisol production is tightly controlled through a negative feedback mechanism, whereby elevated cortisol levels inhibit corticotropin-releasing hormone (CRH) release from the hypothalamus and adrenocorticotropic hormone (ACTH) secretion from the pituitary, thereby modulating further hormone synthesis.

Mechanisms of Cortisol Elevation in Acute Stroke

Hypothalamic and Limbic Activation

Ischemic damage involving critical regulatory regions such as the hypothalamus, insular cortex, and limbic system can directly stimulate central stress pathways. These structures are integral to coordinating autonomic, emotional, and endocrine functions. Injury to these areas may impair

normal inhibitory modulation and intensify hypothalamic output, leading to enhanced activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system.

The insular cortex plays a particularly important role in autonomic control. Infarcts affecting the insula—especially within the right hemisphere—have been associated with heightened sympathetic drive, elevated catecholamine levels, and increased cortisol secretion. Right-sided insular strokes, in particular, are frequently linked to autonomic instability, cardiac arrhythmias, and significant blood pressure fluctuations, reflecting amplified neuroendocrine activation. These findings highlight that the anatomical location of the lesion, in addition to infarct volume, significantly influences the intensity of systemic stress responses following stroke [10,11].

Inflammatory Cytokine Stimulation

Acute stroke provokes a pronounced systemic inflammatory response characterized by elevated concentrations of proinflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). These mediators are produced by activated microglia within the brain, infiltrating leukocytes, and peripheral immune tissues following cerebral ischemia. Although this inflammatory reaction initially contributes to debris clearance and tissue repair, excessive or persistent activation can exacerbate secondary neuronal damage and compromise the integrity of the blood–brain barrier.

Among these cytokines, IL-6 plays a pivotal role in linking inflammatory and neuroendocrine responses. It can cross the blood–brain barrier or act via circumventricular organs to stimulate hypothalamic activity, leading to increased corticotropin-releasing hormone (CRH) secretion. This subsequently enhances adrenocorticotropic hormone (ACTH) release from the pituitary gland and promotes cortisol synthesis in the adrenal cortex. In this way, IL-6 serves as a critical mediator connecting systemic inflammation with activation of the hypothalamic–pituitary–adrenal (HPA) axis, thereby amplifying the stress response in acute stroke [12,13]. This dynamic establishes a bidirectional interaction between inflammatory processes and endocrine activation.

Sympathetic–Adrenal Interaction

Acute stroke is accompanied by significant sympathetic overactivation, leading to increased levels of circulating catecholamines, particularly adrenaline and noradrenaline. This response arises from stimulation of central autonomic networks, including the hypothalamus and brainstem, as part of the coordinated stress reaction to cerebral injury.

The resulting catecholamine surge elevates heart rate, blood pressure, and myocardial oxygen consumption, which may initially support cerebral perfusion during the acute phase. However, excessive or sustained sympathetic activation can promote blood pressure fluctuations, cardiac arrhythmias, myocardial injury, and disturbances in cerebral autoregulation. Catecholamines also interact closely with the hypothalamic–pituitary–adrenal (HPA) axis, stimulating hypothalamic activity and potentiating further cortisol release. In this way, sympathetic overactivity constitutes a central element of the systemic neuroendocrine response to acute stroke and can significantly affect both neurological and cardiovascular outcomes [14].

Biological Effects of Cortisol in Acute Stroke

Metabolic Dysregulation

Cortisol is a key mediator of metabolic adaptation during acute stress, facilitating gluconeogenesis, lipolysis, and protein catabolism. It enhances hepatic glucose output by upregulating gluconeogenic enzymes and increasing the availability of substrates such as amino acids and glycerol. At the same time, cortisol induces peripheral insulin resistance, limiting glucose uptake in skeletal muscle and adipose tissue.

Cortisol also stimulates lipolysis in adipose tissue, releasing free fatty acids, and promotes proteolysis in skeletal muscle, supplying additional amino acids for hepatic glucose production. Although these processes are initially protective—ensuring adequate energy availability during physiological stress—they contribute to the development of stress hyperglycemia in acute stroke. Hyperglycemia has been linked to larger infarct volumes, lactic acidosis within ischemic brain tissue, disruption of the blood–brain barrier, and unfavorable neurological outcomes [8].

Post-stroke hyperglycemia is independently associated with increased infarct size and poorer clinical prognosis. Elevated glucose levels during the acute phase intensify neuronal injury by promoting anaerobic glycolysis in ischemic regions, leading to excessive lactate accumulation and intracellular acidosis. The resulting acidic environment aggravates cellular dysfunction and accelerates neuronal death within the ischemic penumbra.

Hyperglycemia further aggravates ischemic injury by promoting oxidative stress, impairing endothelial function, and compromising the integrity of the blood–brain barrier. These effects increase the likelihood of cerebral edema and hemorrhagic transformation. Elevated glucose levels may also disrupt cerebral autoregulation and diminish the efficacy of reperfusion therapies. Clinical evidence consistently demonstrates that patients presenting with high admission glucose—irrespective of pre-existing diabetes—experience more frequent complications, higher mortality rates, and poorer functional outcomes. These observations underscore the critical importance of early glucose monitoring and appropriate glycemic control in the management of acute stroke [15]. In this context, elevated cortisol may indirectly exacerbate ischemic damage through its contribution to stress-induced metabolic disturbances.

Immunosuppression and Infection Risk

Stroke-induced immunodepression is a well-established consequence of acute cerebral injury, characterized by suppression of both innate and adaptive immune responses. Soon after stroke onset, patients often exhibit lymphopenia, reduced monocyte and natural killer cell activity, and a shift in cytokine balance toward an anti-inflammatory phenotype. This immunosuppressive state is largely mediated by activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, resulting in elevated catecholamine and cortisol levels.

Although this response may initially help limit excessive inflammation and secondary neuronal damage, it simultaneously increases vulnerability to infections—most notably pneumonia and urinary tract infections—which are frequent post-stroke complications. These infections are strongly associated with prolonged hospitalization, impaired functional recovery, and higher mortality rates. Cortisol plays a central role in this process by inhibiting lymphocyte proliferation, suppressing cytokine production, and weakening immune surveillance [8].

Elevated cortisol levels have been specifically linked to a higher risk of post-stroke pneumonia, one of the most serious complications of acute ischemic stroke. Excess glucocorticoid exposure impairs T-cell function, reduces natural killer cell activity, and promotes an anti-inflammatory cytokine profile. When combined with stroke-related factors such as dysphagia, decreased consciousness, and impaired cough reflex, cortisol-mediated immunosuppression creates a permissive environment for respiratory infections. Clinical studies indicate that patients with higher early cortisol concentrations are more likely to develop infections, which in turn contribute to worse functional outcomes and increased mortality. Thus, elevated cortisol may function both as a marker of stroke severity and as a mediator of infection risk following stroke [16,17].

Effects on the Brain

Glucocorticoids are integral to the regulation of neuronal survival, synaptic plasticity, and adaptive stress responses. Under normal physiological conditions, cortisol contributes to energy homeostasis, modulates neurotransmitter activity, and preserves neuronal stability. It also plays a role in cognitive functions such as learning and memory through its actions on hippocampal and cortical networks.

However, excessive or prolonged cortisol exposure may have deleterious effects, particularly in the context of acute ischemic stroke. Elevated glucocorticoid levels can increase glutamate release and inhibit its reuptake, thereby intensifying excitotoxicity—one of the principal mechanisms underlying ischemic neuronal injury. This process promotes intracellular calcium overload, mitochondrial impairment, oxidative stress, and activation of apoptotic signaling pathways. Persistent hypercortisolemia may also disrupt synaptic plasticity and suppress neurogenesis, thereby limiting neural repair and functional recovery.

Consequently, although glucocorticoids are vital for acute stress adaptation, sustained cortisol elevation during stroke may aggravate neuronal damage and impede long-term neurological recovery [18]. Experimental evidence further indicates that chronic glucocorticoid excess heightens the susceptibility of hippocampal neurons to ischemic injury [19].

Cardiovascular Effects

Cortisol increases vascular sensitivity to catecholamines by upregulating adrenergic receptors and strengthening vasoconstrictor signaling pathways. This action elevates peripheral vascular tone and helps maintain blood pressure during acute stress. However, in acute ischemic stroke (AIS), excessive cortisol release may lead to maladaptive cardiovascular effects rather than protective responses.

High cortisol levels have also been linked to endothelial dysfunction, manifested by decreased nitric oxide availability, heightened oxidative stress, and impaired vasodilatory capacity. Such alterations compromise cerebral autoregulation and disturb microvascular blood flow. Through potentiation of catecholamine activity and deterioration of endothelial function, cortisol may contribute to increased blood pressure variability and cardiovascular instability. In the context of AIS, these hemodynamic fluctuations can exacerbate ischemic damage, raise the likelihood of hemorrhagic transformation, and adversely affect neurological outcomes [20].

Cortisol as a Prognostic Biomarker

Association with Stroke Severity

Several studies have demonstrated that higher admission cortisol levels correlate with greater neurological deficit and infarct size. Barugh et al. reported that elevated plasma cortisol was associated with increased mortality and poor outcome after stroke [5]. Saini et al. similarly found that high cortisol predicted adverse outcomes independently of initial stroke severity [6].

Prediction of Mortality

In a prospective cohort study, elevated cortisol levels measured within 24 hours of stroke onset were significantly associated with increased short-term mortality [7]. Persistently elevated cortisol has also been linked to worse long-term survival [21].

Functional Recovery

Higher early cortisol levels have been associated with poorer functional outcomes measured by the modified Rankin Scale at follow-up [6,5]. This suggests that cortisol may serve as an independent prognostic indicator.

Serum vs Salivary Cortisol

Serum Cortisol

Serum cortisol measurement is widely available but reflects total cortisol, including protein-bound fractions. Acute stress from venipuncture may influence results.

Salivary Cortisol

Salivary cortisol reflects free, biologically active hormone and provides a non-invasive alternative [22]. It is particularly useful for repeated or diurnal measurements. However, timing of collection is critical due to circadian variation.

Interaction with Other Stress Biomarkers

Cortisol functions within a complex biological network and does not operate independently in the systemic response to acute ischemic stroke. It shares a bidirectional interaction with catecholamines [14]; sympathetic activation promotes cortisol secretion, while cortisol, in turn, augments vascular responsiveness to adrenergic stimulation. Cortisol is also closely associated with inflammatory markers such as C-reactive protein (CRP) [12] and interleukin-6 (IL-6) [13], both of which increase after cerebral ischemia. IL-6 stimulates activation of the hypothalamic–pituitary–adrenal axis, thereby enhancing cortisol release, whereas CRP reflects the magnitude of systemic inflammation secondary to tissue injury. Furthermore, elevated cortisol concentrations have been linked to greater blood pressure variability [23], likely through its effects on vascular tone and endothelial integrity. In view of these interconnected pathways, a multimarker strategy incorporating cortisol alongside inflammatory, autonomic, and hemodynamic indicators may offer greater prognostic precision than isolated cortisol assessment alone.

Limitations of Current Evidence

Despite promising findings regarding cortisol as a prognostic biomarker in acute ischemic stroke, several important limitations must be acknowledged. Many studies are constrained by small sample sizes, reducing statistical power and limiting generalizability. There is considerable heterogeneity in the timing of cortisol measurement, with some studies assessing levels at admission, others within 24–72 hours, and few performing serial assessments, making comparisons difficult. Variability in assay techniques—such as differences between serum and salivary measurements or immunoassay versus ELISA methods—further complicates standardization and interpretation of results. In addition, longitudinal studies examining long-term cortisol dynamics and functional outcomes remain limited. Importantly, elevated cortisol levels may primarily reflect the severity of brain injury and the magnitude of the stress response rather than directly mediating poor outcomes, raising questions about causality and therapeutic implications.

Therapeutic Implications

Although cortisol suppression itself is not an established therapeutic strategy in acute ischemic stroke, interventions aimed at attenuating excessive systemic stress responses may provide clinical advantages. Careful glycemic management can help minimize the harmful consequences of cortisol-driven stress hyperglycemia, while prompt detection and prevention of infections may reduce the impact of cortisol-related immunosuppression. Preserving circadian rhythm through regulated sleep–wake patterns and appropriate scheduling of clinical interventions may also support stabilization of hypothalamic–pituitary–adrenal (HPA) axis function and prevent further disruption of cortisol secretion [24].

Instead of focusing solely on cortisol reduction, a more comprehensive strategy targeting the broader neuroendocrine and inflammatory cascade may yield better outcomes. Future investigations should emphasize integrated neuroendocrine profiling that incorporates hormonal, inflammatory, and autonomic parameters, along with the development of individualized stress-modulation approaches based on patient-specific physiological and stroke-related characteristics.

CONCLUSION

Cortisol is a central mediator of the neuroendocrine stress response in acute ischemic stroke. Elevated cortisol levels

correlate with stroke severity, increased complications, and poor functional outcomes. As a measurable and biologically significant biomarker, cortisol holds promise for improving prognostic assessment in acute stroke. However, standardization of measurement protocols and large-scale prospective studies are required to clarify its clinical utility.

Declaration by Authors

Ethical Approval: Not applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Isha Atam, Shraddha Singh, Satish Kumar, Nikhil Gupta. Stress biomarkers in acute stroke: cortisol as a prognostic indicator. *Int J Health Sci Res.* 2026; 16(2):341-349. DOI: *10.52403/ijhsr.20260238*

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